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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/717,381	11/19/2003	L.H. Mahishi	A33943-I 066123.0124	8908

21003 7590 03/14/2005

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EXAMINER	
PAK, YONG D	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/717,381	MAHISHI ET AL.	
	Examiner	Art Unit	
	Yong D Pak	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,7,9-11 and 13-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,7,9-11 and 13-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/19/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application is a divisional of 09/772,304, now issued as U.S. Patent No. 6,756,222.

The preliminary amendment filed on November 17, 2003, canceling claims 1-5, 8 and 12, amending claims 6-7, 9-11 and 13 and adding claims 14-15, has been entered.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on November 19, 2003 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Drawings

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

Specification

Examiner notes that applicants have not updated the relationship of the instant application to its parent application (09/772,304) that has matured into a US patent (U.S. Patent No. 6,756,222). Examiner urges applicants to amend said information by providing the US patent number in response to this Office action.

Applicant is required to comply with the sequence rules by inserting the sequence identification numbers of all sequences recited within the claims and/or

specification. It is particularly noted that the sequences in Figure 8 lack sequence identification numbers. See particularly 37 CFR 1.821(d).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-7 and claims 9-11 and 13-15 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6 and 7 recite the phrase "nucleic acid encoding a poly-beta-hydroxybutyrate biosynthetic pathway". The phrase is unclear because a "poly-beta-hydroxybutyrate biosynthetic pathway" is not a protein and therefore, a nucleic acid cannot encode it. Examiner has interpreted that the phrase refers to a nucleic acid encoding a poly-beta-hydroxybutyrate synthase and urges applicants to clarify the phrase in response to the Office Action.

Claim 6 and claims 7, 9-11 and 13-15 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 recites the phrase "which expresses poly-beta-hydroxybutyrate". The phrase is unclear because a "poly-beta-hydroxybutyrate" is not a protein and therefore, it cannot not be expressed by the transformant in the claim. Examiner has interpreted that the phrase refers to a transformant expressing a poly-beta-hydroxybutyrate synthase and urges applicants to clarify the phrase in response to the Office Action.

Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 recites the phrase "poly-beta-hydroxybutyrate biosynthetic pathway is a 4.826 Kb fragment". The phrase is unclear because a "poly-beta-hydroxybutyrate biosynthetic pathway" is not a nucleic acid. Examiner has interpreted that the phrase refers to a nucleic acid encoding a poly-beta-hydroxybutyrate synthase and urges applicants to clarify the phrase in response to the Office Action.

Claims 6-7, 9-11 and 13-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6-7, 9-11 and 13-15 are drawn to a method of producing poly-beta-hydroxybutyrates (PHB) using a microorganism comprising a polynucleotide encoding a PHB synthase. The claims are unclear to the Examiner because the method in the claims fails to recite the substrates used in producing the PHBs and steps in contacting

the substrate with the enzyme. It is unclear to the Examiner if the substrates are also produced in the transformed microorganism of claim 6 (iii) or if the substrates are present in the medium recited in claim 6 (iv). In the context of the above, Examiner takes the position that these claims are incomplete for omitting essential elements, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted elements are: substrates, such as the hydroxyalkanoic acid monomers, used for producing PHBs. Examiner also takes the position that these claims are incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: step of contacting the enzyme and a substrate.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-7, 9, 13, 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 6-7, 9, 13, 15 are drawn to a method of producing poly-beta-hydroxybutyrate by using a host cell comprising a polynucleotide encoding a

Streptomyces aureofaciens NRRL2209 poly-beta-hydroxybutyrate (PHB) synthase. The claims encompass any or all recombinants, variants and mutants of polynucleotides encoding a *Streptomyces aureofaciens* NRRL2209 poly-beta-hydroxybutyrate (PHB) synthase. Therefore, the claims are drawn to a method of producing PHBs using a genus of polynucleotides having any structure. The specification only teaches one species of a polynucleotide encoding a poly-beta-hydroxybutyrate (PHB) synthase, the polynucleotide having the nucleic acid sequence of SEQ ID NO:1 encoding a poly-beta-hydroxybutyrate (PHB) synthase from *Streptomyces aureofaciens* NRRL2209. One species is not enough and does not constitute a representative number of species to describe the whole genus and there is no evidence on the record of the relationship between the structure of a *Streptomyces aureofaciens* NRRL2209 PHB synthase gene and the structure of any recombinants, variants and mutants of a *Streptomyces aureofaciens* NRRL2209 PHB synthase gene. Therefore, the specification fails to describe a representative species of the genus comprising any or all variants and mutants of a polynucleotide encoding a *Streptomyces aureofaciens* PHB synthase used in the method of producing PHBs.

Given this lack of description of the representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the inventions of claims 6-7, 9, 13, 15.

Claims 6-7, 9, 13, 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing PHB using a host cell comprising the polynucleotide having the nucleic acid of SEQ ID NO:1, does not reasonably provide enablement for a method of producing PHB using a host cell comprising any or all variants and mutants of a polynucleotide encoding a *S. aureofaciens* PHB synthase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. (see the interpretation of the phrase "nucleic acid encoding a poly-beta-hydroxybutyrate biosynthetic pathway" in the rejection under 35 U.S.C. 112, 2nd paragraph).

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 6-7, 9, 13, 15 are drawn to a method of producing poly-beta-hydroxybutyrate by using a host cell comprising a polynucleotide encoding a *Streptomyces aureofaciens* NRRL2209 poly-beta-hydroxybutyrate (PHB) synthase. The claims encompass any or all recombinants, variants and mutants of polynucleotides encoding a *Streptomyces aureofaciens* NRRL2209 poly-beta-hydroxybutyrate (PHB)

synthase. Therefore, the claims are drawn to a method of producing PHBs using a genus of polynucleotides having any structure. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of any or all variants and mutants of a polynucleotide encoding a *S. aureofaciens* PHB synthase, broadly encompassed by the claims.

Since the encoded amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a method for producing PHB using a host cell comprising the polynucleotide of SEQ ID NO:1. It would require undue experimentation of the skilled artisan to produce PHB using a host cell comprising any or all variants, mutants and recombinants of a polynucleotides encoding a *S. aureofaciens* PHB synthase for use in producing PHB. It would require undue experimentation of the skilled artisan to make and use the claimed variants and mutants of a polynucleotide encoding a *S. aureofaciens* PHB synthase. In view of the great breadth of the claim, amount of experimentation required to make the claimed polynucleotides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure, the claimed invention would

require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polynucleotides encompassed by the claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass a method for the enzymatic production of PHB using any or all mutants and variants of a polynucleotide encoding a *S. aureofaciens* PHB synthase, because the specification does not establish: (A) regions of the structure of a PHB synthase which may be modified without affecting PHB synthase activity; (B) the general tolerance of a PHB synthase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated

with the scope of the claims broadly including a method for the production of PHB using a host cell comprising any or all variants and mutants of a polynucleotide encoding a *S. aureofaciens* PHB synthase. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any or all mutants and variants of a polynucleotide encoding a S. aureofaciens PHB synthase having the desired biological characteristics recited in the claim is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 6-7, 9-11, 13 and15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention appears to employ novel microorganism E. coli JM109 PTA 1529. Since the microorganism is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The claimed plasmids' sequences used to make the recombinant microogansim are not fully disclosed, nor have all the sequences required for their construction been shown to be publicly known and freely available. The enablement requirements of 35 U.S.C. 112 may be satisfied by a deposit of the microorganism. The specification does not disclose a repeatable process to obtain said microorganism and it is not apparent if the

DNA sequences to make the microorganism are readily available to the public. Accordingly, it is deemed that a deposit of these plasmids should have been made in accordance with 37 CFR 1.801-1.809.

It is noted that applicants have deposited the organisms but there is no indication in the specification as to public availability. If the deposit was made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strain has been deposited under the Budapest Treaty and that the strain will be available to the public under the conditions specified in 37 CFR 1.808, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance or compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

1. during the pendency of this application , access to the invention will be afforded to the Commissioner upon request;

2. upon granting of the patent the strain will be available to the public under the conditions specified in 37 CFR 1.808;

3. the deposit will be maintained in a public repository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and

4. the deposit will be replaced if it should ever become inviable.

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Yong D. Pak
Patent Examiner 1652

Manjunath Rao
Primary Examiner 1652